PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/013693	17.11.2004	17.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/46, C07K7/08, A61K38/10, A61K38/17

Applicant
UNIVERSITY OF ULSTER

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

10/579581
International application No.
PCT/EP2004/013693

IAP20 Rec'd PCT/PTO 17 MAY 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-9 (partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-9 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. Invention 1, claims 1-9 (partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-6,9
	No:	Claims	1,7,8
Inventive step (IS)	Yes:	Claims	2,5,6
	No:	Claims	3,4,9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/013693

Re Item IV.

Lack of unity of invention

1. This Authority considers that there are 9 inventions covered by the present set of claims

The following inventions are not so linked as to form a general inventive concept:

Invention 1, claims 1-9 (partially): Insulinotropic peptides isolated from the skin secretions of the frog Agalychnis and defined by SEQ ID Nos: 1-3; modified forms of said peptides; the use of said peptides in the preparation of a medicament; and, pharmaceutical compositions comprising said peptides.

Invention 2, claim 1-9 (all partially): Insulinotropic peptides isolated from the skin secretions of the frog Bombina and defined by SEQ ID Nos: 4 and 5; modified forms of said peptides; the use of said peptides in the preparation of medicaments; and, pharmaceutical compositions comprising said peptides.

Invention 3, claims 1-9 (all partially): Idem as invention 2 but where the peptide is defined by SEQ ID NO: 6.

Invention 4, claims 1-9 (all partially): Idem as invention 2 but where the peptide is defined by SEQ ID NO: 7.

Invention 5, claims 1-9 (all partially): Idem as invention 1 but where the peptides are isolated from the frog Phyllomedusa and defined by SEQ ID Nos: 8 and 9.

Invention 6, claims 1-9 (partially): An insulinotropic peptide isolated from the skin secretions of the frog Rana and defined by SEQ ID NO: 10; modified forms of said peptide; the use of said peptide in the preparation of a medicament; and, pharmaceutical compositions comprising said peptide.

Invention 7, claims 1-9 (all partially): Idem as invention 6 but where the peptides are defined by SEQ ID Nos: 11 and 17.

Invention 8, claims 1-9 (all partially): Idem as invention 6 but where the peptides are defined by SEQ ID Nos: 12, 15 and 16.

Invention 9, claims 1-9 (all partially): Idem as invention 6 but where the peptides are defined by SEQ ID Nos: 13 and 14.

2. The claims of the present application relate to insulinotropic peptides isolated from frog skin secretions.

In assessing whether the requirements of unity of invention of an application are met, identification of the technical features that each solution to a technical problem contributes over the prior art (special technical features) must be made. If then a technical relationship between the solutions, involving one or more of the same special technical features, can be recognised, the requirements of unity of invention are said to be met.

Regarding the prior art, Abdel-Wahab, Y. H. A., et al., (2002), Diabetologia, vol. 45 (Supplement 2), A178, Conference: 38th Annual Meeting of the European Association for the Study of Diabetes (EASD); Budapest, Hungary; September 01-05, 2002 and Abdel-Wahab, Y. H. A., et al., (2001), Diabetologia, vol. 45 (Supplement 1), pp. A135, Conference: 37th Annual Meeting of the European Association for the Study of Diabetes; Glasgow, Scotland, UK; September 09-13, 2001 both describe the isolation and characterisation of insulinotropic peptides from frog skin secretions.

Therefore, in light of this prior art, the first problem identified in the present application can be considered as the provision of further insulinotropic peptides isolated from frog skin secretions.

The first solution to this first problem is given by invention 1, claims 1-9 (partially): insulinotropic peptides isolated from the skin secretions of the frog Agalychnis and defined by SEQ ID Nos: 1-3; modified forms of said peptides; the use of said peptides in the preparation of a medicament; and, pharmaceutical compositions comprising said peptides.

The second problem identified in the present application can be considered as the provision of further insulinotropic peptides isolated from the frog Bombina.

The first solution to this second problem is given by invention 2, claim 1-9 (all partially): insulinotropic peptides isolated from the skin secretions of the frog Bombina and defined by SEQ ID Nos: 4 and 5; modified forms of said peptides; the use of said peptides in the preparation of medicaments; and, pharmaceutical compositions comprising said peptides.

The second solution to this second problem is given by invention 3, claims 1-9 (all partially): idem as invention 2 but where the peptide is defined by SEQ ID NO: 6.

The third solution to this second problem is given by invention 4, claims 1-9 (all partially): idem as invention 2 but where the peptide is defined by SEQ ID NO: 7.

The second solution to the first problem is given by invention 5, claims 1-9 (all partially): idem as invention 1 but where the peptides are isolated from the frog Phyllomedusa and defined by SEQ ID Nos: 8 and 9.

The third problem identified in the present application can be considered as the provision of further insulinotropic peptides isolated from the frog Rana.

The first solution to this third problem is given by invention 6, claims 1-9 (partially): an insulinotropic peptide isolated from the skin secretions of the frog Rana and defined by SEQ ID No: 10; modified forms of said peptide; the use of said peptide in the preparation of a medicament; and, pharmaceutical compositions comprising said peptide.

The second solution to this third problem is given by invention 7, claims 1-9 (all partially): idem as invention 6 but where the peptides are defined by SEQ ID Nos: 11 and 17.

The third solution to this third problem is given by invention 8, claims 1-9 (all partially): idem as invention 6 but where the peptides are defined by SEQ ID Nos: 12, 15 and

16.

The fourth solution to this third problem is given by invention 9, claims 1-9 (all partially): idem as invention 6 but where the peptides are defined by SEQ ID Nos: 13 and 14.

3. As no technical features can be distinguished which, in the light of the prior art, could be regarded as special technical features on which an unifying concept could be based, there is no single inventive concept underlying the plurality of claimed inventions of the present application.

Therefore, an objection to lack of unity of invention has to be raised under Rule 13.1 PCT. Consequently, a distinction of separate inventions has been made (1-9), based on technical features. The resulting separate inventions, as presently identified, have been grouped according to the order in which they have been claimed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Basis of this written opinion

1.1 Since the subject-matter of inventions 2-9 has not been searched this written opinion has been restricted to the subject-matter for which an International Search Report has been drawn up, namely, invention 1 (SEQ ID Nos: 1-3).

2. Citations

2.1 The documents mentioned in the present written opinion are numbered as in the International Search Report i.e. D1 corresponds to the first document of the search report, etc.

3. Novelty (Article 33(2) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject matter of claims 1, 7 and 8 is not new in respect to the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

3.2. (a). The subject-matter of claim 1 is unclear (Article 6 PCT) (see Item VIII. 1). Should claim 1 refer to the peptides, *per se*, the subject-matter of said claim would lack novelty (Article 33(2) PCT) in light of D2 which discloses a peptide having 53.846% identity in 13 amino acid residues overlap (50% identity using ClustalW) to SEQ ID NO:1 of the present application.

(b). Furthermore, if claim 1 is intend to refer to the first medical use of the peptides (see item VIII. 1 below) then the subject-matter of said claim would also lack novelty (Article 33(2) PCT) in light of D2 which discloses the first medical use of a peptide a peptide having 53.846% identity in 13 amino acid residues overlap (50% identity using ClustalW) to SEQ ID NO:1 of the present application.

3.3 Document D2 also discloses a pharmaceutical composition comprising the therein described peptide. Therefore, D2 also anticipates the subject-matter of claims 7 and 8 (Article 33(2) PCT).

3.4 The subject-matter of claims 2-6 and 9 meets the requirements of Article 33(2) PCT because the subject-matter of said claims does not appear to be disclosed in the available prior art documents.

4. Inventive step (Article 33(3) PCT)

4.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 3, 4 and 9 does not involve an inventive step (Rule 65(1)(2) PCT).

4.2 The modifications to the not novel peptide of claim 1, as set forth in claims 3 and 4, would be obvious to skilled person faced with the apparent technical problem to be solved. Consequently, claims 3 and 4 cannot be considered inventive (Article 33(3) PCT).

4.3 The formulation of the not novel pharmaceutical composition of claim 8 with the agents of claim 9 would fall within the standard practise of the skilled person and is, therefore, not inventive (Article 33(3) PCT).

4.4 Claims 2, 5 and 6 fulfil the requirements of Article 33(3) PCT because the available prior art neither discloses nor suggests the use of the proteins defined by SEQ ID Nos: 1-3 for stimulating insulin secretion and pancreatic beta cell function.

5. Industrial applicability (Article 33(4) PCT)

1. The subject-matter of claims 1-9 has industrial applicability (Article 33(4) PCT).

Re Item VIII

Certain observations on the international application

1. The subject-matter of claim 1 is unclear (Article 6 PCT) as it is not apparent whether the claim is directed to either the peptides, *per se*, or the first medical use of said peptides.

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